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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,404	08/18/2003	Takayuki Tanaka	59753 (48185)	3999

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,404	TANAKA ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. By Amendment filed 08/02/06, claims 2-3 have been cancelled; claims 1 and 4 have been amended; and claim 5 has been newly added. Claims 1-5 are currently pending for prosecution on the merits.

2. The new claim 5 is directed to the same subject matter as the previously examined claims 1-4. Accordingly, claim 5 will be included in the group of claims that were previously rejected.

Summary of Action

3. The rejection of claims 1 and 4 under 35 U.S.C. 112, first paragraph (scope of enablement) is maintained for the reasons of record.

4. The rejection of claims 1 and 4 under 35 U.S.C. 102(b) as being anticipated by Nishi et al. (US 4857542) is maintained for the reasons of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the restenosis or neointimal formation caused by coronary angioplasty, percutaneous transluminal coronary angioplasty (PTCA) or a coronary-artery bypass graft (CABG), does not reasonably provide enablement for the term "prevention

and/or therapy wall injury...". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The inventions relate to a method of preventing or treating arterial wall injury which is caused by coronary angioplasty or coronary artery bypass graft. The instant specification broadly defines the term "arterial wall injury" as "neointimal formation, the restenosis or reocclusion of vascular lumens or decrease in elasticity and flexibility" (page 12, lines 3-5).

Websters II Dictionary defines the term "prevent" as "anticipate or counter in advance, to keep from happening". The interpretation of the instant claims allows for the complete cure and eradication or total elimination of arterial wall injury caused by coronary angioplasty or coronary artery bypass graft by the administration of said compound (3-methyl-1-phenyl-2-pyrazolin-5-one".

The scope of the instantly claimed "arterial wall injury" caused by coronary angioplasty or coronary artery bypass graft encompasses not only neointimal formation or restenosis caused by PTCA or CABG, but also various other diseases characterized by "decrease in elasticity and flexibility" or "reocclusion of vascular lumens" subsequent to coronary angioplasty or coronary artery bypass graft, for example hypertension.

With respect to the scope of enablement for "prevention",

There are no known compounds of similar structure which have been demonstrated to prevent or cure the claimed conditions encompassed by the instant claims. Since this assertion is contrary to what is known in medicine, proof must be provided that this assertion has merits. The existence of such a "magic bullet" is contrary to our present understanding of pharmacology. Thus, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" or completely cure or eradication effect.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant compounds.

The specification discloses study showing the efficacy of 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone) in decreasing neointimal formation caused by balloon injury to the abdominal aorta or carotid artery of the animal (i.e., rabbits or rat)(Examples). However, there is no demonstrated correlation the tests and results apply to prevent the claimed conditions embraced by the instant claims.

Since the efficacy of the claimed compound(s) in preventing "arterial wall injury" or "restenosis or neointimal" caused by coronary angioplasty or coronary artery bypass graft, mentioned above cannot be predicted from a priori or the instant specification but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for "arterial wall injury" which is caused by coronary angioplasty or coronary artery bypass graft,

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the therapeutic utility of the instant compound.

The specification discloses study showing the efficacy of 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone) in decreasing neointimal formation caused by balloon injury to the abdominal aorta or carotid artery of the animal (i.e., rabbits or rat)(Examples). However, there is no demonstrated correlation the tests and results apply to the arterial wall diseases embraced by the instant claims, for example hypertension.

For example, hypertension and restenosis are recognized in the art as totally different conditions, and the skill artisan would not have known that the administration of said compound having the activity of reducing neointimal formation would provide therapeutic utility in the treatment of said "arterial wall injuries" including hypertension, without undue amount of the experimentation.

In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Nishi et al. (US 4857542).

Nishi teaches the administration of compound(s) represented by the formula I (i.e., 3-methyl-1-phenyl-2-pyrazolin-5-one) to mammals including human (column 4, lines 2-7) to treat or prevent circulatory disorders (abstract; column 5, line 59; claim 10), wherein said compound(s) is administered at (oral) a dose of 1 to 100mg 1 to 3 times/day, (intravenous injection) at a dose of 0.01 to 10 mg 2 to 5 times/day, or (intrarectal administration) at a dose of 1 to 100mg 1 to 3 times/day (column 9, lines 9-18).

Although Nishi is silent about the prophylactic utility of said compound in preventing arterial wall injury, namely caused by coronary angioplasty or coronary-artery bypass graft (CABG) or restenosis or neointimal formation after percutaneous transluminal coronary

angioplasty (PCTA), percutaneous coronary intervention (PCI) or coronary-artery bypass graft (CABG), such prophylactic utility deems to be inherent the referenced method. The prior art directing administration of the same compound(s) to mammals (i.e., human), in overlapping dosage amounts, inherently possessing the claimed prophylactic utility as disclosed by the applicant anticipates the applicant's invention.

Response to Arguments

7. Applicant's arguments filed August 02, 2006 have been fully considered but they are not persuasive.

There is no argument present in the applicant's response for the examiner's rejection of the claims (claims 1-4) under 35 USC 112, first paragraph. Although the applicant made the amendment to the claims, but failed to point out disagreements with the examiner's contentions about the instantly claimed "prophylactic utility" as well the treatment of "arterial wall" diseases encompassed by the instant claims. Thus, in absence of applicant's rebuttal evidence and argument, this rejection is maintained.

In response to the rejection of the claims 1-4 under 35 USC 102(b) rejection as being anticipated by Nishi et al. (US 4857542), applicant's argument in the response takes the position that one of ordinary skill in the art would not envisage using 3-methyl-1-phenyl-2-pyrazolin-5-one to prevent or provide therapy for an arterial wall injury, which is caused by coronary angioplasty or coronary-artery bypass graft (CABG), based on the extremely large number of circulatory diseases and the large possible number of compounds of formula (I). Applicant states: "One of ordinary skill in the art would not envisage the utilization of 3-methyl-2-phenyl-2-

pyrazolin-5-one to treat arterial wall injury, based on a reading of Nishi. Regardless of the number of disorders that is recited in the specification, Nishi et al. does not provide for a method of preventing or treating an arterial wall injury. Therefore, at least one element of the claimed subject matter is lacking in Nishi, and Nishi does not anticipate the instant claims".

This argument is not found persuasive. Unlike the applicant' argument, Nishi discloses 3-memthyl-1-phenyl-2-pyrazolin-5-one (compound 1) as one of the most preferred species of the formula I that is useful as the prophylactic and therapeutic agent for circulatory disorders including myocardial ischemia or ischemia disease (claim 10; Example 2; Tables 2-3).

The interpretation of the instant claims allows for the inclusion of any mammals including human. In other words, the instantly claimed humans are a genus to human having extremely large numbers of physical conditions. Since Nishi's disclosed circulatory disorder, (e.g., ischemic disease) anticipates the instantly claimed human containing that species, the Nishi's teaching directed to the administration of the same compound (3-memthyl-1-phenyl-2-pyrazolin-5-one), in overlapping dosage amount (the instant invention discloses "oral administration, 0.1 to 100 mg/kg body weight per day, preferably 0.5 to 50 mg/kg body weight per day, and in the case of parenteral administration, 0.01 to 100mg/kg body weight per day and preferably 0.1 to 10 mg/kg body weight" in the last paragraph of page 9 to the bridging paragraph in top of the page 10; if patient is 70kg body weight, oral dosage is within 7 to 7000 mg per day, preferably 3.5 to 3500 mg per day and in case of parenteral 0.7 to 7000 mg per day, preferably 7 to 700 mg per day which overlaps with the referenced "(oral) a dose of 1 to 100mg 1 to 3 times/day, (intravenous injection) at a dose of 0.01 to 10 mg 2 to 5 times/day, or (intrarectal administration) at a dose of 1 to 100mg 1 to 3 times/day), to the same patient

inherently possessing the claimed prophylactic utility as disclosed by the applicant anticipates the applicant's invention.

Although Nishi is silent about the instantly claimed prophylactic utility of said compound in preventing arterial wall injury caused by coronary angioplasty (PCTA) or coronary artery bypass graft (CABG), namely restenosis or neointimal formation after PCTA or PCI or CABG, such prophylactic utility deems to be inherent to the referenced method.

Conclusion

8, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. 9

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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VICKIE KIM
PRIMARY EXAMINER